REMARKS

Applicants have amended claim 51 to improve its form and to more particularly point out certain embodiments of Applicants' invention. Support for this amendment is found throughout the specification, for example, at Example 1, page 59-64; Example 2, pages 65-69; and page 50, lines 1-5.

Applicants have added claims 56-58. All of these claims depend directly or indirectly from claim 51. Support for these claims is found throughout the specification, for example at original claims 12-14.

No new matter has been introduced. After entry of Applicants' amendments, claims 51-52 and 54-55 are pending. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below.

Double Patenting Rejection

Claims 51-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of application no. 10/922,374 (the '374 application). Applicants respectfully traverse.

Applicants have amended claim 51 of the instant application to recite a method of producing a blastula or morula comprising the step of introducing mitochondria or mitochondrial DNA derived from cell or cells of a human donor cell into a bovine oocyte. Claims 52-55 depend directly or indirectly from claim 1, and thus include all of the limitations of claim 1. None of the pending claims in the '374 application claim a method as reflected in the amended claims, and thus the instant application does not claim subject matter that is the same as or obvious in view of the invention claimed in the '374 application. Accordingly, Applicants request withdrawal of this rejection.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 51-53 are rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the enablement requirement. The Examiner asserts that in view of the unpredictable

state of the art with regard to cross species NT, the fate of the mtDNA from the donor cell, the importance of mtDNA in embryonic development, the lack of guidance or teaching with regard to incorporation of the donor mtDNA into the oocyte, the lack of teaching or guidance provided by the specification with regard to the isolation of embryonic or stem-like cells or the use of the claimed method, as well as the state of the art of producing ES cells, it would have required undue experimentation for one of ordinary skill in the art to practice the claimed invention. Applicants respectfully traverse.

As the Examiner indicated, the Wands factors are the appropriate criteria for assessing whether the level of experimentation needed to practice the claimed invention is undue. The Wands factors include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the subject matter at issue, (5) the state of the prior art, (6) the relative skill of those in the art, and (7) the predictability or unpredictability of the art.

An evaluation of the instant application in view of the Wands factors demonstrates that the disclosure in the instant application is enabling for the claimed subject matter. The nature of the subject matter at issue is a method of producing a blastula or morula comprising the step of introducing mitochondria or mitochondrial DNA derived from human cell or cells into a bovine oocyte. The breadth of the claims encompasses utilizing any human donor cell with any bovine oocyte, to produce a morula or blastula.

Guidance of the specification/existence of working examples.

Applicants point out that the specification provides extensive guidance to one of skill in the art. For example, the instant application teaches methods of performing cross species SCNT using human donor cells and a bovine oocyte on pages 19-35 and 59-64 and the use of mitochondria or mitochondrial DNA on pages 50 and 64-69. Although Applicants do not provide working examples of the complete method of claim 51, Applicants provide an example of cross species SCNT (Example 1) and a protocol for isolating mitochondria (Example 2). Compliance with the enablement requirement does not necessitate the disclosure of working examples as long as "the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." *In re Borkowski*, 442, F.2d 904, 908, 164 USPQ 642,645 (CCPA 1970)." Because the relative skill of those in the art is extremely high and because

the specification provides a detailed description of the claimed methods, the specification need not disclose an actual working example further exemplifying the detailed teachings of the specification to enable one of skill in the art to practice the claimed invention.

State of the art/ unpredictability of the art.

Cross Species NT Unit Formation. As the Examiner states, the low level of efficiency in producing interspecies NT units found in the specification is consistent with results found in the art. This low level of efficiency is standard in the nuclear transfer and embryonic stem cell art and does not evince unpredictability or otherwise undermine enablement. The level of efficiency of a method may indicate that one of skill in the art may need to perform the method multiple times or that a level of experimentation will be needed to achieve the desired result. However, especially when the practitioner knows that the method is inefficient, this is not surprising and does nothing to undermine the practitioners confidence that the method will work – albeit only a certain percentage of the time.

Applicants contend that regardless of the level of efficiency, the methods taught by the application are predictable and reproducible as evidenced by Chang et al. Chang et al., Fertil Steril. 2003 Dec;80(6):1380-7, (Chang) demonstrate that karyotypically normal blastocyst cells can be generated using cross species nuclear transfer by inserting human somatic nuclei into bovine oocytes using the methods taught by applicants. Chang describes at pages 1381-1382 performing the steps of: obtaining bovine oocytes, physically dissociating the cumulus cells from the oocytes, enucleating the oocytes by micromanipulation, depositing a donor somatic human cell into the oocyte by micromanipulation using a pipette, fusing the donor/oocyte complex by electric pulses, activating oocytes, and culturing the nuclear transfer units. Chang did not use any additional steps beyond those taught by the instant application. Accordingly, Chang supports Applicants' contention that the claimed invention is enabled based on the specification and the level of skill in the art. One of skill in the art could readily follow, without undue experimentation, the detailed procedure provided in the specification to obtain a blastula or morula by inserting a human cell or nucleus into a bovine oocyte.

The instant claims have been amended to a method of producing a blastula or morula comprising the step of introducing mitochondria or mitochondrial DNA derived from human cell or cells into a bovine oocyte. Detailed description of the claimed method can be found throughout the

specification, for example, in Example 1 on pages 59-64. Applicants' amendments are not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. Accordingly, one of skill in the art could readily practice the claimed invention throughout its scope without undue experimentation based on the detailed procedure provided in the specification.

Mitochondrial DNA. The Examiner argues that Mastromonaco et al. (Biol Reprod. 2007 Mar;76(3):514-23) shows that introduction of mtDNA is unpredictable, but applicants disagree. The benefits of introducing donor-derived mitochondria or mitochondrial DNA do not necessarily require incorporation of the DNA into the oocyte. Even if the long term stability of donor-derived mitochondria is in doubt in particular species as indicated by Jiang et al. (Frontiers in Bioscience, 11: 1425-1432, May 1, 2006) and Chang, the short term stability of donor-derived mitochondria is undisputed. It is apparent from the prior art in the field that incompatibility of the nucleus with mitochondria during interspecies SCNT complicates cloning, and thus that supplementing SCNT procedures with mitochondria may be useful for improving cloning methods.

Morula or blastula embryo. The Examiner argues that the only contemplated purpose of applicants' elected invention is to produce embryonic or stem-like cells. Applicants disagree. The specification states on page 14, lines 9-11 that cells produced by the methods of the invention may be used to study differentiation and for assay purposes.

Amount of experimentation.

The state of the art indicates that the efficiency of SCNT is variable between different species and that the level of efficiency may vary depending on the particular donor-recipient combination. For example, Chang produce many blastocysts with abnormal numbers of chromosomes, as well as normal blastocysts (see Table 3, Figure 1B).

Applicants contend that a low level of efficiency does not constitute a lack of enablement or indicate that the level of experimentation required to practice the claimed invention is undue. Even though a procedure may not be highly efficient, the success rate may be sufficient for the purposes of the invention. Further, enablement does not require that one of skill in the art can practice the claimed invention without any experimentation, but rather that the amount of experimentation required is not undue. In fact, the MPEP and prevailing case law reflect the appreciation that even

the need for extensive experimentation is consistent with the enablement requirement. See, MPEP 2164.06.

> The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether undue experimentation is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Applicant additionally note that the remaining steps of the presently claimed method for introducing mitochondria or mitochondrial DNA into the oocyte do not require undue experimentation.

The foregoing analysis of the Wands factors support Applicants' contention that the claims are enabled throughout their scope. The teachings of the instant application truly provide the public with methods for a producing a blastula or morula comprising the step of introducing mitochondria or mitochondrial DNA derived from cell or cells of a human donor cell into a bovine oocyte. Skilled practitioners can readily performed the presently claimed methods based on the teachings of the instant application and the level of skill in the art without undue experimentation.

In evaluating the enablement of the claimed subject matter, both the courts and the MPEP have acknowledged that some experimentation is permissible, as long as that experimentation is not undue (MPEP 2164.04). "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). However, the courts have been clear that the determination of whether undue experimentation is required should not be made based solely on the time and cost involved in conducting such experimentation. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should

proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). "Time and expense are merely factors in this consideration and are not the controlling factors." *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

In the present case, Applicants note that post-filing date evidence supports Applicants' position that the claims are enabled throughout their scope. Clearly, the tools available to skilled artisans permitted the practice of the claimed invention without undue experimentation. The practice of nuclear transfer methods is time consuming, expensive, and inefficient. However, that is the expectation of skilled practitioners in this field and does not evince that the practice of the claimed methods requires undue experimentation.

MPEP 2164.04 outlines the criteria for evaluating enablement. "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

The reasoning outlined in MPEP 2164.04 is well supported by case law stating that "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

Furthermore, as exemplified by *In re Strahilevitz*, a broadly enabling disclosure need not include a single working example (*In re Strahilevitz*, 668 F.2d 1229, 212 USPQ 561 (CCPA 1982)). In *Strahilevitz*, the court reversed the Appeal Board's holding of non-enablement, and pointed out that the provisions of 35 U.S.C. 112, first paragraph, do not require that Applicants provide working

examples. This sentiment was echoed in *In re Wright* which held that to comply with 35 U.S.C. 112, first paragraph, "[n]othing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."

Finally, both the courts and the Board of Patent Appeals and Interferences have issued opinions which recognize that common sense and prosecutorial expediency contradict decisions that would require Applicants to disclose every last detail of an invention. "Not every last detail [of an invention need] be described [in a patent specification], else patent specifications would turn into production specifications, which they were never intended to be." (*In re Gay*, 390 F.2d 769, 774, 135 USPQ 311, 316 (CCPA 1962)). These sentiments were reiterated by the Board in their decision in *Staehelin v Secher*. Citing *In re Gay*, the Board concluded that "the law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 U.S.C. 112, first paragraph." (*Staehelin v Secher*, 24 USPQ 2d 1513, 1516 (Bd. Pat. App. & Int. 1992).

Applicants contend that the maintenance of this rejection is contrary to the standards for evaluating enablement outlined in the MPEP, and upheld by the Federal Circuit and the Board of Patent Appeals and Interferences.

In accordance with MPEP 2164.05, when making a determination as to the enablement provided for the claimed invention, the evidence must be considered as a whole. Furthermore, "the evidence provided by the applicant need not be conclusive but merely convincing to one skilled in the art." (MPEP 2164.05). Applicants contend that this burden has been amply satisfied.

Applicants' amendments are not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. Applicants' amendments are believed to obviate the rejection, and reconsideration and withdrawal of the rejection are requested.

Co-pending applications

The Examiner is obviously aware of the existence of co-pending application number 10/922,374, discussed in the Office Action mailed December 1, 2006 in reference to the double patenting rejection. Applicants take this opportunity to note that prosecution is on-going in co-pending application number 10/922,374, and the most recent action is an Advisory Action mailed May 16, 2007.

Applicants take this opportunity to make the Examiner aware of the existence of co-pending application number 10/981,137. Applicants note that prosecution is on-going in co-pending application number 10/981,137, and the most recent action is a Final Office Action mailed August 8, 2007.

The Examiner is obviously aware of the existence of co-pending application number 10/329,979, discussed in the Office Action mailed December 1, 2006 in reference to the double patenting rejection. Applicants take this opportunity to note that prosecution is on-going in co-pending application number 10/329,979, and the most recent action is a Non-Final Office Action mailed September 13, 2007.

CONCLUSION

In view of the foregoing amendments and remarks, applicants request that the Examiner reconsider and withdraw all outstanding rejections and grant allowance of the pending claims.

Applicants request that any additional fee required for consideration of this submission be charged to **Deposit Account No. 18-1945**, from which the undersigned is authorized to draw under Order No. 103080-P08-058.

The Examiner is invited to telephone applicants representatives regarding any matter that may be handled by telephone to expedite allowance of the pending claims.

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Respectfully submitted,

By _____

Matthew P. Vincent, Ph.D., J.D.
Registration No.: 36,709
Melissa S. Rones, J.D., Ph.D.
Registration No.: 54,408
ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys/Agents For Applicant